B. Accordingly, it is clear that Claims 5, 6, 7, and 8 remain pending in this application and the Examiner is respectfully requested to correct the record.

As preliminarily amended, the claims of this divisional application are directed to particularly preferred embodiments of the invention which are improved methods of isolating a peptide, polypeptide, or protein molecule using affinity particles in which a detergent is specifically employed to reduce loss of the affinity particles and, thereby, improve particle handling and yields of molecules isolated by such methods (see, e.g., Table 1, p. 21; Table 2, p. 22; Table 3, p. 23; Table 4, p. 25; and Table 6, p. 29 in the specification).

The Invention

The claimed invention is based on Applicants' discovery of how to reduce or prevent particle loss in affinity procedures for isolating a peptide, polypeptide, or protein molecule in which affinity particles are manipulated. According to the invention, adding detergent to one or more steps in an affinity procedure prior to and/or contemporaneously with a step in which the affinity particles are manipulated (e.g., collected, separated, or washed) will reduce loss of the affinity particles compared to the same procedure carried out without the benefit of detergent treatment (see, e.g., Examples section, pp. 20-29 of the specification). Hence, Applicants' claimed invention improves all prior art affinity procedures for isolating a peptide, polypeptide, or protein molecule in which affinity particles are manipulated in the absence of a detergent, which as Applicants have demonstrated invariably results in particle loss and, thereby, reduced and inconsistent yields. As explained below, none of the references or any combination thereof cited by the Examiner discloses the problem of losing affinity particles during manipulations in a procedure to isolate a peptide, polypeptide, or protein molecule. Furthermore, none of the references or the cited combination thereof teaches or suggests Applicants' discovery of how to reduce or prevent loss of affinity particles in such isolation procedures by contacting the affinity particles with a detergent.

Rejections Under 35 U.S.C. § 102(e)

In the Office Action, the Examiner rejected Claims 2-3, 13-18, 19, 23, 24, 32, 34, 44-50, 54, 55, 62-66, and 68 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,942,391 (issued August 24, 1999, "Zhang"). The Examiner also rejected Claims 2-3, 13-18, 19, 23, 24, 32, 34, 44-50, 54, 55, and 62-66 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,466,577 (issued November 14, 1995, "Weisburg"). In particular, the Examiner alleges that each of Zhang and Weisburg demonstrates each step in the claimed methods for isolating or separating a peptide, polypeptide, or protein molecule wherein loss of affinity particles is reduced by

contacting the particles with a detergent. Applicants respectfully traverse the rejection for the reasons explained below.

The law regarding anticipation of a claim by a printed publication is clear. For anticipation under 35 U.S.C. § 102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in § 2131 of the Manual of Patent Examining Procedure (MPEP):

> **"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**
>
> " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

Zhang

The Zhang patent describes methods for detecting a target nucleic acid from a pathogenic microorganism or from patients with genetic diseases or cancer (see, e.g., col. 3, lines 9-16; col. 5, line 61-col. 6, line 20 of Zhang). The methods of Zhang use multiple nucleic acid probes, including a "capture probe", which is attached to the surface of paramagnetic particles and which binds to a target nucleic acid molecule (see, e.g., col. 3, lines 52-59; Figure 1 of Zhang).

Nowhere does Zhang teach or suggest how to reduce loss of affinity particles during manipulation of such particles to improve an affinity isolation procedure for a peptide, polypeptide, or protein molecule of interest. A person of ordinary skill in the art who reads Zhang is never informed of the problem of particle loss or of how to reduce loss of affinity particles when used in an isolation procedure. Zhang does not provide any example that shows the benefit of using detergent in affinity methods as taught and demonstrated in Applicants' specification (see, e.g., Examples section, pp. 20-29 of the specification) or as recited in the pending claims in a procedure for isolating a peptide, polypeptide, or protein molecule.

Weisburg

The Weisburg patent describes nucleic acid probes that hybridize to specific target sequences in the 16S ribosomal RNA of *Borrelia* bacterial species, such as *B. bugdoferi*, the etiological agent of Lyme's Disease. Weisburg also describes the use of such probes to detect *Borrelia* target nucleic acid in dot blots (see, e.g., Example 1, col. 6, line 66-col. 7, line 31 of Weisburg) and sandwich hybridization schemes where a "capture" probe binds a target sequence

and a "detector" probe signals the binding of the target sequence (see, e.g., Example 2, col. 7, lines 35-62). Example 3 of Weisburg describes a sandwich hybridization protocol to diagnose Lyme's disease from a blood sample, in which the capture probe is linked to a magnetic particle (see, col. 8, lines 6-12). However, nowhere does Weisburg teach or suggest use of a detergent in an isolation method that uses affinity particles in order to reduce loss of affinity particles in subsequent steps of a procedure for isolating a peptide, polypeptide, or protein molecule.

In contrast to Zhang and Weisburg, Applicants' invention provides affinity methods for isolating a peptide, polypeptide, or protein molecule in an affinity procedure in which the loss of affinity particles during manipulations of the particles is reduced by contacting the particles with detergent. Zhang and Weisburg each discloses only methods of detecting nucleic acids, not a peptide, polypeptide, or protein molecules as in Applicants' claimed invention, and *nowhere does Zhang or Weisburg provide any disclosure of the problem of losing affinity particles during manipulations of the particles*. Furthermore, neither Zhang nor Weisburg teaches or suggests that loss of affinity particles during manipulations can be reduced or prevented by contacting the particles with a detergent.

The Examiner argues anticipation of Applicants' claimed invention by finding specific steps in the procedure of Zhang or of Weisburg that include a detergent. For example, the Examiner states that Zhang describes the use of a buffer containing a detergent to wash paramagnetic beads containing nucleic acid hybrid molecules on their surface (col. 40, line 6 of Zhang). In Weisburg, the Examiner relies on a description that the detergent SDS could be used in a buffer to lyse cells in a procedure to isolate RNA using magnetic beads derivatized with oligo-thymidine residues (col. 8, lines 3-11 of Weisburg). Neither of the examples in Zhang or Weisburg provides a teaching relevant to Applicants' invention. That detergent can be used in a lysis buffer is not relevant to the process of controlling particle loss. Neither reference recognizes the problem of or describes Applicants' solution for reducing particle loss in affinity procedures for isolating a peptide, polypeptide, or protein molecule by contacting the particles with a detergent. Neither reference, moreover, makes any statement that the affinity particles were conserved during the described nucleic acid isolations, which, after all, is the entire object of Applicants' teaching alleged to be anticipated in the art.

The Examiner has not shown how persons of ordinary skill in the art who read Zhang or Weisburg would ever be aware of the problem of losing affinity particles during manipulations or of Applicants' affinity methods in which loss of affinity particles can be reduced by contacting the particles with a detergent.

The above comments clearly show that neither Zhang nor Weisburg disclose Applicants' claimed methods of isolating a peptide, polypeptide, or protein molecule using affinity particles which reduce loss of affinity particles when the particles are manipulated. Thus, both references fail to teach each and every element of Applicants' claimed methods. Clearly, neither Zhang nor Weisburg are effective references for anticipating Applicants' claimed procedures. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections the claims under 35 U.S.C. § 102(e).

Rejections Under 35 U.S.C. § 103(a)

In Section 7 on p. 6 of the Office Action, the Examiner rejected certain claims as obvious under 35 U.S.C. § 103(a) over Weisburg. There is a discrepancy in the first two paragraphs of Section 7 as to precisely which claims are rejected. Applicants assume that the Examiner meant to direct the rejection to Claims 2, 3, 13-20, 23-26, 32-34, 44-50, 54-57, and 62-66.

In Section 8 of the Office Action, the Examiner rejected Claims 2, 3, 13-19, 21, 23, 24, 29-30, 32, 34, 44-50, 52, 54, 55, and 60-66, and 68 as obvious over Zhang in view of U.S. Patent No. 5,798,442 (issued August 25, 1998, "Gallant").

In Section 9 of the Office Action, Claims 2, 3, 13-19, 22-28, 30, 32, 34, 44-50, 52, 54, 55, 58, 59, 62-66, and 68 were rejected as obvious over Zhang in view of U.S. Patent No. 4,009,213 (issued February 22, 1977, "Stein").

In Section 10 of the Office Action, Claims 2, 3, 13-19, 23, 24, 32, 34, 44-50, 54, 55, and 62-68 were rejected as obvious over Zhang in view of U.S. Patent No. 5,385,959 (issued January 31, 1995, "Tsaur").

In Section 11 of the Office Action, the Examiner rejected Claims 2, 3, 13-19, 23, 24, 32, 34, 44-50, 54, 55, 62-66, and 68-69 as obvious over Zhang in view of U.S. Patent 6,180,548 B1 (issued January 30, 2001, "Taoda").

For the reasons discussed below, Applicants respectfully traverse each of the rejections.

As noted above, neither Weisburg nor Zhang teaches Applicants' claimed methods for isolating a peptide, polypeptide, or protein molecule in an affinity procedure in which the loss of affinity particles during manipulations of the particles is reduced by contacting the particles with a detergent. Thus, to the extent that each of the rejections in the Office Action begins with the statement that Weisburg or Zhang "teaches" Applicants' claimed methods, the rejections misstate the facts. Furthermore, however, none of the references alone or in the combinations made by the Examiner teaches or suggests Applicants' improvement over prior art procedures of using affinity particles in methods of isolating a peptide, polypeptide, or protein molecule which employ a detergent to reduce particle loss.

As noted above, the primary references Zhang and Weisburg describe nucleic acid probes and their use to detect target nucleic acid molecules related to various diseases, not methods of isolating a peptide, polypeptide, or protein molecule comprising reducing loss of affinity particles during manipulations of the particles. The Examiner has not shown how persons of ordinary skill in the art who have read Zhang or Weisburg would be aware of the problem of losing affinity particles during manipulations or would know how to reduce such particle according to Applicants' claimed procedures for isolating a peptide, polypeptide, or protein molecule.

Weisburg is insufficient to render Applicants' claimed invention *prima facie* obvious. Again, Weisburg describes nucleic acid probes that hybridize to specific sequences found in the 16S ribosomal RNA of *Borrelia* bacterial species, especially *B. burgdorferi*, which causes Lyme's Disease. Weisburg describes the use of such probes for the clinical diagnosis of Lyme's disease in humans and other animals (see, e.g., col. 3, lines 51-67). Such probes may be linked to a magnetic particle as described in Example 2 of Weisburg. However, nowhere does Weisburg contemplate, teach, or suggest Applicants' claimed methods for improving affinity methods for isolating a peptide, polypeptide, or protein molecule by using detergent to reduce particle loss that otherwise occurs during manipulation of the affinity particles. Weisburg does not even recognize the problem of particle loss in various prior art affinity procedures or provide any suggestion or motivation to be combined with any of the other references cited by the Examiner to solve the problem of particle loss.

Applicants respectfully submit that it is clear that Weisburg does not make Applicants' claimed improvements over prior art procedures *prima facie* obvious. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections based on Weisburg under 35 U.S.C. § 103(a).

The Basis for Combining Zhang with Secondary References

The Examiner relied on Zhang as a primary reference in combination with each of Gallant, Stein, Tsaur, and Taoda to reject claims as *prima facie* obvious under 35 U.S.C. § 103(a). At the outset, Applicants note the well-established standard regarding combining references as a basis for rejecting claims as *prima facie* obvious. Obviousness cannot be established using Applicants' own disclosure as a guide to merely selecting and reconstructing the claimed invention from elements in the prior art. The patent law is clear:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577; 221

> USPQ 929, 933 (Fed.Cir. 1984), citations omitted, emphasis in original).

Evidence of a suggestion or motivation to combine references may be found in the references themselves or in the knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed.Cir. 1988); *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992). The motivation to combine may derive from many sources, however, the range of possible sources that may serve as evidence for a motivation to combine references "does not diminish the requirement for actual evidence. That is, the showing [of a motivation to combine] must be clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617, 1999 WL 246572 (Fed.Cir. 1999).

Omitting a particular statement of the suggestion or motivation to combine prior art references to make a claimed invention simply amounts to hindsight reconstruction based on an inventor's own teachings. As the Court of Appeals for the Federal Circuit noted in *In re Dembiczak*:

> "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability -- the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999; 50 USPQ2d 1614, 1617; 1999 WL 246572 (Fed.Cir. 1999).

It is contrary to the law to reject claims as obvious by using hindsight reconstruction, in which elements are merely gathered from the references using the framework provided by an inventor's disclosure:

> "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075; 5 USPQ2d 1596, 1600 (Fed.Cir. 1988).

Zhang describes methods employing multiple probes to detect a target nucleic acid molecule, either by amplifying copies of selected sequences in the target molecule ("RAM") or by using amplified numbers of signal probes to emit a detectable signal ("HSAM") to indicate that a target nucleic acid molecule has been bound by a probe for the target (see, e.g., col. 6, lines 4-8, Figs. 1 and 10 of Zhang). One type of probe is a "capture-amplification" probe described by Zhang which may be linked to a paramagnetic particle (see, e.g., col. 7, lines 25-30; Figs. 1 and 10 of Zhang). However, Zhang does not recognize in any way the problem of affinity particle

loss as addressed and solved by Applicants' methods. Furthermore, Zhang does not provide a suggestion or motivation to be combined with any other reference cited by the Examiner to make Applicants' claimed improved methods. Accordingly, Zhang alone cannot render Applicants' claimed methods obvious under 35 U.S.C. § 103(a), and any combination of Zhang with another reference(s) is improper unless the references provide their own suggestion or motivation for such combination and further provide a cure for the multiple deficiencies of Zhang.

In the Office Action, the Examiner sought to make Applicants' claims *prima facie* obvious based on the combination of Zhang with any of several other references. However, as shown in detail below, not only do the other references relied on by the Examiner fail to teach or suggest Applicants' claimed improvement in affinity procedures, but they also fail to provide the required evidence of a motivation to be combined with Zhang to suggest Applicants' claimed invention. Moreover, as is made clear below, even if the references are considered together for the sake of argument, the result is an odd combination of disparate methods, not a disclosure of Applicants' claimed invention that advances the art of affinity procedures for isolating a peptide, polypeptide, or protein molecule by reducing particle loss.

Zhang and Gallant

Gallant describes a cysteine proteinase called apopain, which appears to play a key role in promoting apoptosis, and peptidyl derivative compounds that inhibit apopain (see, e.g., col. 1, lines 6-15; col. 10, lines 17-col. 14, line 56 of Gallant). Apopain cleaves the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) in the early onset of apoptosis (see, e.g., col. 2, lines 36-47 of Gallant).

The Examiner relies on Gallant to provide a teaching of the use of the zwitterionic detergent CHAPS in an HPLC affinity purification method at col. 22, line 33-col. 23, line 27. The section of Gallant cited by the Examiner describes a purification scheme for apopain that involves applying a cytosolic fraction of THP-1 cells to a DEAE-5PW HPLC column that has been pre-equilibrated in a Tris/HCl buffer comprising 0.1% (w/v) CHAPS zwitterionic detergent. Proteins were then eluted with a linear gradient of NaCl in Tris/HCl buffer also comprising 0.1% (w/v) CHAPS.

However, the method of Gallant is an HPLC column method and not an affinity method in which particles are manipulated or separated from solution and subject to loss during such manipulation. That is, the particles being confined to an HPLC column, particle manipulation and loss cannot be a technical problem addressed by Gallant. Thus, no teaching in Gallant can be relevant here, and the Examiner's reliance on Gallant simply because of the mention of CHAPS is inappropriate and provides no contribution to a rejection for obviousness.

In addition, Gallant is devoid of any suggestion or motivation to be combined with Zhang to make Applicants' methods. Furthermore, even if Zhang is combined with Gallant, the result is the combination of two very different methods used to achieve two different purposes: a standard HPLC method to purify apopain proteinase vs. a multi-probe method of detecting target nucleic acid molecules. Clearly, Gallant adds nothing to advance the teachings of Zhang to arrive at Applicants' claimed methods. Accordingly, Applicants respectfully submit that the combination of Zhang and Gallant does not make out a *prima facie* case of obviousness to reject Applicants' claims.

Zhang and Stein

The method of Stein is a continuous process for separating mixtures of fatty alcohols that relies on modifying fatty alcohol chemistry, including converting the fatty alcohol components in a mixture into different forms that have different melting points, then separating the subsequently formed liquid and solid forms of the converted fat compounds using aqueous wetting agent solutions (see, e.g., col. 3, line 55-col. 4, line 2 of Stein). Any of variety of wetting agents may be used in the method of Stein (see, e.g., col. 5, line 59-col. 6, line 24 of Stein). The Examiner relies on Stein as a teaching for the use of the cationic detergent dodecyl trimethyl ammonium chloride (see, e.g., col. 6, lines 22-24 of Stein). However, Stein only teaches the use of this agent as a "cationic...water-soluble compound which lower[s] the surface tension of the aqueous solutions." That is, the teaching relied on by the Examiner relates to surface tension of aqueous solutions, and particle manipulation and loss cannot be a technical problem addressed by Stein. Thus, no teaching in Stein can be relevant here, and the Examiner's reliance on Stein simply because of the mention of dodecyl trimethyl ammonium chloride is inappropriate and provides no contribution to a rejection for obviousness. Stein does not describe an improved affinity method for isolating a peptide, polypeptide, or protein molecule with reduced loss of affinity particles during manipulations of the particles. Thus, Stein provides no recognition of the problem addressed by Applicants' claimed invention. Furthermore, Stein provides no suggestion or motivation to be combined with Zhang to suggest Applicants' claimed affinity methods, which use detergent in conjunction with affinity particles to reduce particle loss during steps in which the particles are manipulated.

As with the other combinations set forth by the Examiner, even if Zhang is combined with Stein, the result is a confusing mixture of methods: In this case, a method of using multiple nucleic acid probes to detect target nucleic acid sequences and a continuous process of separating fatty alcohols that relies on the particular chemistry of "fatty substances". Thus, even when combined, which is improper as a matter of law, the result of Zhang and Stein is not Applicants'

claimed method for improving affinity procedures for isolating a peptide, polypeptide, or protein molecule by using detergent to reduce loss of affinity particles. Clearly, Stein cannot cure the deficiency of the primary reference Zhang to make Applicants' claimed methods *prima facie* obvious, and accordingly reconsideration and withdrawal of the rejection based on Zhang and Stein is respectfully solicited.

Based on the above comments and the amendments to the claims, Applicants respectfully submit that none of the references, alone or in the combinations set forth in the Office Action, renders Applicants' claims *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.

Zhang and Tsaur

With respect to combining Zhang and Tsaur, the Examiner states:

> "Zhang et al teach the method of claims 2-3, 13-18, 19, 23, 24, 32, 34, 44-50, 54, 55 and 62-66 and 68 are [sic] as described above.
>
> "Zhang et al do not teach the method wherein the polyethylene polymer is a polyvinyl alcohol.
>
> "Tsaur et al. teach the method wherein the polyethylene polymer is a polyvinyl alcohol. (Column 11, lines 11-44 and Claims 1-3).
>
> "It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the polyethylene polymer polyvinyl alcohol of Tsaur et al in the method of Zhang et al since Tsaur et al state, 'Indeed such reactions are well known in the art and widely used in protein purification (Column 11, lines 34-35)'. An ordinary artisan would have been motivated by the express statement of Stein et al [sic] to utilize the cationic detergents of Tsaur et al in the method of Zhang et al in order to improve the protein purification and in order to achieve the express advantage of a method, as noted by Tsaur et al, which is well known in that art and widely used in protein purification." (paragraphs 2-5, Section 10, pp. 9-10 of the Office Action, Paper No. 4).

As noted above, Zhang describes a method that employs multiple nucleic acid probes to detect a target nucleic acid molecule, not Applicants' claimed method of isolating a peptide, polypeptide, or protein molecule in which loss of affinity particles during manipulations is reduced by contacting the particles with a detergent. In addition, if Stein was meant to be included in this rejection, Applicants have also explained above that Stein describes an improved continuous process for separating mixtures of fatty alcohols that relies on modifying fatty alcohol chemistry, that Stein fails to provide any motivation or suggestion to be combined with Zhang,

and that Stein cannot cure the deficiencies of Zhang to make Applicants' claimed invention *prima facie* obvious.

Nevertheless, according to the above quote from the Office Action, the Examiner appears to cite Tsaur as providing a reference for using polyethylene polymer, as supposedly motivated by a suggestion in Stein, in the method of Zhang to make Applicants' claimed methods *prima facie* obvious. However, Tsaur describes capsules of a composite polymer that is resistant to heavy duty liquid (detergent) compositions, not methods of isolating a peptide, polypeptide, or protein molecule. A capsule of Tsaur is designed to protect entrapped enzymes that are sensitive to degradation in the heavy duty liquid. The composite polymer is able to deliver the entrapped enzyme when the heavy duty liquid is diluted with water. This is art that has nothing to do with the claims under consideration.

The portion of Tsaur cited by the Examiner is a paragraph describing various hydrophilic polymers that can reversibly cross-link with the hydrophobic polymer core of the composite detergent compositions (see, col. 11, lines 12-44 of Tsaur). Such hydrophilic polymers include various proteins that are known to form reversible cross-links with certain cross-linking agents such as tannic acid, trichloroacetic acid and ammonium sulfate, which reversible cross-linking reactions "are well known in the art and widely used in protein purification" (see, col. 11, lines 30-35 of Tsaur). Clearly, this simple description of the desired reversible cross-linking reaction of certain hydrophilic proteins useful in the composite polymer of heavy duty liquid compositions of Tsaur *in no way provides a suggestion or motivation that Tsaur be combined with Zhang.* Nor does this irrelevant passage make the combination of Tsaur and Zhang more applicable to Applicants' claimed methods. As noted above, in the absence of a link between the technology of Zhang and the different technology discussed in Tsaur, combination of the references is improper; and, also as noted above, even the improper combination of Zhang and Tsaur is unable to suggest even the field of Applicants' invention.

Even if Zhang is combined with Tsaur, the Examiner has not shown how one of ordinary skill in this art would take a method of detecting target nucleic acids (Zhang) and the composite polymers used for detergents (Tsaur) to make Applicants' claimed invention, which provides improved affinity methods of isolating a peptide, polypeptide, or protein molecule by reducing affinity particle loss when the particles are manipulated. Clearly, the composite polymers of Tsaur do not cure the deficiencies of the nucleic acid detection probes and methods of Zhang to make Applicants' claimed invention *prima facie.* Accordingly, reconsideration and withdrawal of the rejection are respectfully solicited.

Zhang and Taoda

As noted above, Zhang describes methods and probes for detecting target nucleic acids. Taoda describes an environment purifying material in which particles of titanium oxide (photocatalyst) coated with calcium phosphate are used to decompose proteins, bacteria, and viruses. Titanium oxide is known to have certain reduction-oxidation properties. The calcium phosphate coating has pores and is used to protect and improve the durability of the light and water sensitive titanium dioxide. Taoda explains how this material works as an environment purifying material by decomposing and removing adsorbed proteins, bacteria, viruses, etc. (see, e.g., col. 4, lines 10-14 of Taoda). Clearly, neither Zhang or Taoda provides any suggestion or motivation for the references to be combined. They relate to different fields of technology, and neither relates directly to the present invention. Accordingly, the combination of Zhang and Taoda is respectfully submitted to be improper for the purposes of this examination.

Even if Zhang could be properly combined with Taoda (which it cannot), the Examiner has not shown how one of ordinary skill in this art would be able to take a method of detecting target nucleic acids (Zhang) and an environment purifying material comprising titanium oxide (Taoda) to approximate the Applicants' claims. Applicants submit that the environment purifying material of Taoda in no way cures the deficiencies of the use of nucleic acid detection probes of Zhang in failing to fairly suggest the methods claimed by Applicants. Accordingly, reconsideration and withdrawal of the rejection are respectfully solicited.

For all of the reasons set forth above, Applicants submit that the references and combinations of references as cited by the Examiner fail to make Applicants' claimed invention *prima facie* obvious under 35 U.S.C. § 103(a). Accordingly, reconsideration and withdrawal of the rejections are respectfully solicited.

CONCLUSION

In view of all of the above comments, Applicants submit that it is clear that none of the references, alone or in any combination composed by the Examiner, teaches or suggests Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejections be withdrawn and Claims 2, 3, 5-8, 13-30, 32, 34, 36-39, and 44-69 be passed to issue.

Respectfully submitted,

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